A Review of Neurologic Complications of Biologic Therapy in Plaque Psoriasis

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PRACTICE POINTS

• Patients with a personal or strong family history of demyelinating disease should be considered for alternative treatment options before initiating anti–tumor necrosis factor (TNF) α therapy.

• Patients on biologic agents, especially TNF-α inhibitors, with subacute or rapidly progressive visual, motor, or sensory changes or a single neurologic deficit may warrant referral to neurology and/or neuroimaging.

Biologic agents have provided patients with moderate to severe psoriasis with treatment alternatives that have improved systemic safety profiles and disease control; however, case reports of associated neurologic complications have been emerging. Tumor necrosis factor α (TNF-α) inhibitors have been associated with central and peripheral demyelinating disorders. Notably, efalizumab was withdrawn from the market in 2009 for causing progressive multifocal leukoencephalopathy (PML). It is imperative for dermatologists to be familiar with the clinical presentation, evaluation, and diagnostic criteria of neurologic complications of biologic agents used in the treatment of psoriasis.

Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a fatal demyelinating neurodegenerative disease caused by reactivation of the ubiquitous John Cunningham virus. Primary asymptomatic infection is thought to occur during childhood, then the virus remains latent. Reactivation usually occurs during severe immunosuppression and is classically described in human immunodeficiency virus infection, lymphoproliferative disorders, and other forms of cancer. A summary of PML and its association with biologics is found in Table 1. Few case reports of TNF-α inhibitor–associated PML exist, mostly in the presence of confounding factors such as immunosuppression or underlying autoimmune disease. Presenting symptoms of PML often are subacute, rapidly progressive, and can be focal or multifocal and include motor, cognitive, and visual deficits. Of note, there are 2 reported cases of ustekinumab associated with reversible posterior leukoencephalopathy syndrome, which is a hypertensive
### TABLE 1. Clinical Presentation and Diagnostic Workup of PML Associated With Biologics

<table>
<thead>
<tr>
<th>Biologic Agent</th>
<th>Incidence of Associated PML</th>
<th>Clinical Presentation</th>
<th>Diagnostic Workup</th>
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<tr>
<td>Efalizumab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 cases in the absence of confounding factors (ie, HIV/AIDS, concurrent immunosuppressive therapy)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Multifocal process resulting in diverse clinical manifestations: visual field defects, cortical blindness (20%–50% of patients and often the presenting manifestation)&lt;sup&gt;9&lt;/sup&gt;, motor weakness, gait abnormalities, incoordination, behavioral and cognitive abnormalities, single neurological deficit</td>
<td>MRI&lt;sup&gt;7&lt;/sup&gt;; CSF studies: PCR for John Cunningham virus DNA; gold standard: brain biopsy&lt;sup&gt;8&lt;/sup&gt;</td>
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<td>Rituximab</td>
<td>1 in 25,000 RA patients&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>TNF inhibitors (infliximab, adalimumab, etanercept)&lt;sup&gt;10-13&lt;/sup&gt;</td>
<td>Unknown</td>
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**Abbreviations:** PML, progressive multifocal leukoencephalopathy; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

<sup>a</sup>Most reported cases of PML associated with biologic agents were in patients treated for nonpsoriatic diseases and have been confounded by the use of other immunosuppressive therapies or were unconfirmed PML.

<sup>b</sup>Approved for moderate to severe plaque psoriasis in 2003 but withdrawn from the market in 2009.

### TABLE 2. Clinical Presentation and Diagnostic Workup of Demyelinating Disorders Associated With Biologics

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Biologic Agent</th>
<th>Incidence of Associated Demyelinating Disorder</th>
<th>Clinical Presentation</th>
<th>Diagnostic Workup</th>
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<tr>
<td>Optic neuritis: inflammatory demyelinating process of the optic nerve</td>
<td>Etanercept</td>
<td>49% of reported cases secondary to anti–TNF-α therapy (N=123)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Onset over several hours and peaking 1–2 wk after initial presentation; pericolic pain; unilateral loss of visual acuity; Uhthoff symptom: exercise/heat-induced deterioration of visual symptoms; Pufreich phenomenon: misperception of direction of movement of an object; ipsilateral afferent pupillary defect; scotoma; optic disc pallor; loss of color vision</td>
<td>Clinical triad: visual loss, pericolic pain, dyschromatopsia&lt;sup&gt;15&lt;/sup&gt;; MRI; CSF analysis</td>
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<td>Infliximab</td>
<td>43% of reported cases secondary to anti–TNF-α therapy (N=123)&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>Adalimumab</td>
<td>7% reported cases secondary to anti–TNF-α therapy (N=123)&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>Multiple sclerosis: autoimmune inflammatory demyelinating disorder of the central nervous system</td>
<td>Etanercept</td>
<td>51% of reported cases secondary to anti–TNF-α therapy (N=55)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Polysymptomatic onset occurring at 15–50 y of age; presenting symptoms include sensory disturbance (paresthesia and alterations in touch; pin-prick, vibration, facial, position, and postural sensations), weakness in the legs (more common) and arms, and visual disturbance&lt;sup&gt;15&lt;/sup&gt;; ataxia; bladder problems; fatigue; Lhermitte sign; Uhthoff symptom (exacerbated by heat); optic neuritis and internuclear ophthalmoplegia</td>
<td>Definitive diagnosis: ≥2 symptomatic attacks (lasting &gt;24 h, separated by at least 1 mo), with at least 1 attack confirmed by objective findings on either neurologic examination, visual evoked potential/response, or MRI; CSF studies</td>
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<td>Adalimumab</td>
<td>27% of reported cases secondary to anti–TNF-α therapy (N=55)&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>Infliximab</td>
<td>20% reported cases secondary to anti–TNF-α therapy (N=55)&lt;sup&gt;17&lt;/sup&gt;</td>
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encephalopathy characterized by headache, altered mental status, vision abnormalities, and seizures.14,15 Fortunately, this disease is reversible with blood pressure control and removal of the immunosuppressive agent.16

Demyelinating Disorders
Clinical presentation of demyelinating events associated with biologic agents are varied but include optic neuritis, multiple sclerosis, transverse myelitis, and Guillain-Barré syndrome, among others.17-28 These demyelinating disorders with their salient features and associated biologics are summarized in Table 2.17-20,22-28 Patients on biologic agents, especially TNF-α inhibitors, with new-onset visual, motor, or sensory changes warrant closer inspection. Currently, there are no data on any neurologic side effects occurring with the new biologic secukinumab.29

Conclusion
Biologic agents are effective in treating moderate to severe plaque psoriasis, but awareness of associated neurologic adverse effects, though rare, is important to consider. Physicians need to be able to counsel patients concerning these risks and promote informed decision-making prior to initiating biologics. Patients with a personal or strong family history of demyelinating disease should be considered for alternative treatment options before initiating anti–TNF-α therapy. Since the withdrawal of efalizumab, no new cases of PML have been reported in patients who were previously on a long-term course. Dermatologists should be vigilant in detecting signs of neurological complications so that an expedited evaluation and neurology referral may prevent progression of disease.

REFERENCES

### Table 2. (continued)

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<thead>
<tr>
<th>Disorder</th>
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<th>Clinical Presentation</th>
<th>Diagnostic Workup</th>
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<tbody>
<tr>
<td>Transverse myelitis: immune-mediated spinal cord disorder with neurologic signs of motor, sensory, and autonomic spinal cord dysfunction</td>
<td>Etanercept&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Associated with systemic autoimmune diseases (ie, RA, scleroderma, SLE); sensory: well-defined (cervical or thoracic) sensory level, below which pain and temperature sensation is altered; motor: initial limb flaccidity followed by hypesthesia and Babinski sign; autonomic: bowel and bladder incontinence, urinary urgency or retention, constipation, sexual dysfunction&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Clinical presentation, spinal MRI, CSF studies</td>
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<td>Guillain-Barré syndrome: acute immune-mediated polyneuropathy characterized by rapidly progressive limb weakness and diminished or absent reflexes</td>
<td>Efalizumab&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Two-thirds of cases have preceding respiratory or gastrointestinal tract symptoms ~3 wk before presentation&lt;sup&gt;24&lt;/sup&gt;; symmetric, rapidly progressive, ascending bilateral weakness of the arms and legs with hypesthesia or areflexia; limb numbness and pain; facial, respiratory, and bulbar muscle weakness; urinary retention and ileus</td>
<td>Clinical presentation, CSF studies, neurophysiology studies</td>
</tr>
</tbody>
</table>

Abbreviations: TNF, tumor necrosis factor; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.


